

Supreme Court Ruling Broadens BRCA Testing Options

By Anna Azvolinsky

The day after Mother's Day, actress Angelina Jolie wrote an op-ed in the *New York Times* revealing her decision to undergo a double mastectomy after learning that she carries a deleterious mutation in the BRCA1 gene. Jolie and women like her who have certain germ-line BRCA1 or BRCA2 mutations are at higher risk for breast and ovarian cancers. Jolie, whose mother died from ovarian cancer, said she wanted other women who may have a familial history of these cancers to be aware of their genetic testing options. She also highlighted that not all women can afford the \$3,000 individual risk assessment the test offers.

The predictive genetic test that screens for mutations in both BRCA genes has been available only through Utah-based Myriad Genetics, a molecular diagnostics company that holds patents on the BRCA genes.

But the Supreme Court has lifted what was a monopoly on BRCA genetic testing, invalidating five of Myriad's BRCA patents. In a unanimous ruling on June 13, the high court deemed isolated genes natural phenomena that companies may not patent.

Still, both plaintiffs and defendants announced that the ruling was in their favor. "The opinion is clear when it comes to isolated genomic DNA. The decision overturns the patent office's policy," said Sandra Park, attorney with the American Civil Liberties Union, who was involved in the case. On the other side, Myriad announced that the decision still upholds 24 of its patents, including claims on methods to analyze the genes. "Those claims around BRCA analysis are strong," said Ron Rogers, spokesperson for Myriad.

But Park pointed out that if the company thought the rest of the patents would allow it to maintain a monopoly, Myriad didn't need to keep fighting the lawsuit. The ACLU filed the initial lawsuit against the validity of Myriad's BRCA patents in 2009, along with the Public Patent Foundation and medical

researchers, clinicians, genetic counselors, patients, and cancer survivors. The case has been argued in several federal courts.

The U.S. Patent and Trademark Office has already issued preliminary guidance on patent filings, stating that the Supreme Court decision would significantly change their policy in reviewing patent claims on naturally occurring DNA sequences.

Broader Access

The decision allows unrestricted research and options for genetic testing, researchers say. "I think it will open avenues for more research and testing for patients as the test becomes cheaper," said Terry Mamounas, M.D., medical director of the Comprehensive Breast Program at M. D. Anderson Cancer Center Orlando. "This is good for patients as long as the tests developed are accurate and detect the whole spectrum of mutations."

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Several companies, including California-based Ambry Genetics and New Jersey-based Quest Diagnostics, announced (as early as the day of the Supreme Court decision) that they will add the BRCA genes to their existing gene panels or offer a stand-alone test. Other companies and institutions are likely to follow.

The University of Washington's BROCA gene panel, which tests for a spectrum of high-risk cancer genes, not just those linked to breast and ovarian cancer, will now include the BRCA genes. The test costs approximately \$3,300 for 52 genes, compared with Myriad's \$3,600 price to test for both mutations and large rearrangements.

Myriad has a two-tiered test, looking first for the most common BRCA mutations. Its second test, called the BRCAAnalysis Large Rearrangement Test (BART), tested for mutations that account for approximately 10% of all BRCA mutations missed by the BRCAAnalysis and became available in 2006. Approximately 80% of insurers cover BART as a secondary test.

A patient (who wished to remain anonymous) fell into a testing coverage black hole when her insurance failed to cover the incremental test. She was diagnosed with cancer in one breast at a young age, followed by cancer in the other breast, and finally ovarian cancer in her early fifties. In 2006, 7 months before BART was available, her BRCA test came back negative. In 2012, her insurance began to cover BART and established the woman as a rare BRCA mutation carrier—but not before her daughter, herself a mother, was diagnosed with advanced, aggressive breast cancer.



Terry Mamounas, M.D.

Too Much Information?

The newer tests and Myriad's own promise to be comprehensive, making stories such as that one rare. In 2014, Myriad aims to launch a 25-gene panel test that will include the BRCA genes.

But as whole-genome sequencing becomes cheaper, single-gene tests and even gene panels could soon become outdated. "I think it is just a matter of time until whole-genome sequencing will be offered routinely," said Mamounas.

But Mamounas warns that such analysis carries risks. Appropriate counseling

about the genetic information is crucial, as is ensuring that only the right patients are tested. “Just because we have this tool doesn’t mean that everyone with breast cancer has a genetic mutation and needs testing. We need to use good judgment and rely on physicians’ and counselors’ inputs to see who should be tested,” said Mamounas.

In response to the recent flurry of news on the topic, the nonprofit ECRI Institute created the BRCA Gene Mutation Resource Center as a public-health service. The institute’s BRCA testing guide that stresses only those women with specific risk factors should be tested.

A Wealth of Information in a Database

Still a concern is the proprietary mutation database Myriad has accumulated from performing more than 1 million tests.

Some of these mutations, referred to as genetic variants of unknown significance, are not fully characterized, and whether they confer cancer risk is not clear. Although Myriad has worked to compile these mutations to understand whether the variants track with disease among family members, the company has not shared this knowledge with the scientific community. That information can help guide decisions for patients, researchers say. “The company should make the database public because it is important for patients to know what their sequenced gene means,” said Mamounas.

Although whether Myriad will make its database publicly available is unclear, researchers are organizing their own efforts. But the U.S. is far behind in using genetic testing as a prevention mechanism, says Olufunmilayo I. Olopade, M.D., professor

of medicine and director of the Center for Clinical Cancer Genetics at the University of Chicago. According to Olopade, the Europe-based CIMBA (Consortium of Investigators of Modifiers of BRCA1/2) has pooled mutation data from more than 40,000 BRCA mutation carriers, but “in the U.S., valuable information is locked away in databases.”

Despite the patent challenges, Olopade said that she and colleagues are creating their own database to assist new test developers. The researchers have been using the BROCA test, but because of Myriad’s BRCA patents, they could not use the data to assist in clinical care until now. “I am hailing this decision [by the Supreme Court] because it will really allow us to use genetics to improve public health.”

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New Tests for Prostate Cancer

By Leslie Harris O’Hanlon

This last year has seen a surge of activity in researching and developing tests to help clinicians better diagnose and treat prostate cancer.

Better tests are needed, many say, to more accurately detect prostate cancer and to help men and their physicians decide what to do about it. A few such tests have become commercially available recently or are poised to do so. But researchers warn that the tests need to pass muster before being adopted for use in the clinic.

“They need to be proven,” said Scott A. Tomlins, M.D., Ph.D., assistant professor of pathology and urology at the University of Michigan at Ann Arbor. “This is an important consideration for clinicians to have: How much does this test improve their clinical decision making, and what will they do with the results of the test?”

Aggressive Disease

Many of the nearly 250,000 men diagnosed with prostate cancer in the United States

annually don’t need treatment because their slow-growing, low-risk tumors are not likely to do them harm. But predicting which tumors will turn aggressive can be difficult with current clinical measures. As a result, many men will have radiation, surgery, or both to treat their prostate cancer. These treatments can cause uncomfortable side effects, including urinary incontinence, bowel function problems, and erectile dysfunction.

“The answer to the prostate cancer controversy is not to stop screening,” said Matthew Cooperberg, M.D., M.P.H., assistant professor of urology and epidemiology–biostatistics at the University of California, San Francisco. “But the answer is to fix overtreatment. We can’t stick our heads in the sand and stop looking for prostate cancer.”

The Oncotype DX prostate cancer test, developed by Genomic Health, analyzes the expression of 17 genes. On the basis of the expression of these genes, men can be categorized as having low-, intermediate-,

or high-risk prostate cancer. Those in the low-risk group could opt for active surveillance, monitoring a patient’s condition through serial prostate-specific antigen (PSA) screening and prostate biopsies rather than for more radical treatment. The test went on sale after Cooperberg presented results of a UCSF validation study at the 2013 American Urological Association annual meeting in San Diego in May. The study involved nearly 400 men who could have gone on active surveillance but chose surgical removal of their prostates. Researchers used the Oncotype test to analyze biopsy tissues from these men and then looked at the men’s medical records to see whether the test accurately predicted which men had prostates showing evidence of aggressive disease. According to the UCSF researchers, the test added clinically meaningful prognostic information and identified more men with low-risk disease who could safely choose surveillance.

“Sixty percent of men diagnosed with prostate cancer have localized prostate